DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 526-6004

June 7, 1999

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED
Mr. Richard K. Kloss
Manager Custom Manufacturing
Shamrock Technologies, Inc.
Foot of Pacific Street
Newark, New Jersey 07114

FILE No.: 99-NWJ-25

Dear Mr. Kloss:

This letter is regarding an inspection of your facility located at Foot of Pacific Street, Newark, New Jersey, by the U.S. Food and Drug Administration (FDA), between the dates of 10/19-27/98. The inspection revealed significant deviations from Current Good Manufacturing Practices (CGMPs), in the micronizing of bulk Sulfanilamide and other active pharmaceutical ingredients (APIs), which resulted in the issuance of a multiple item FDA Form 483 at the completion of the inspection. These deviations cause the APIs that you micronize to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). Although the CGMP regulations under Title 21 Code of Federal Regulations, Parts 210 and 211, are used as guidelines for API processing, Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held in accordance with CGMPs. No distinction is made between active pharmaceutical ingredients and finished pharmaceuticals. Failure to comply with CGMPs constitutes a failure to comply with requirements of the Act.

We have reviewed your comments to the FDA 483 items made at the closeout meeting on 10/27/98, and your 11/23/98 letter submitted to Ms. Regina T. Brown at the FDA's New Jersey District Office. We conclude that these responses lack sufficient detail, explanations, or documentation to adequately address the deviations noted during the October 1998 inspection. Our comments regarding the most significant observations are shown below:

1. You employ a multi-purpose "Clean Room" which is used for micronization/grinding of numerous API's, nutritionals, and industrial chemicals. There is no assurance that the positive pressure air generated by the HVAC system in the "Clean Room" is adequate to prevent cross contamination of the various types of products processed. There is no documented specification for air pressure differentials, and there is no data to establish the levels of positive pressure required to prevent the ingress of industrial chemicals from the warehouse to the "Clean Room."

   Additionally, your room cleaning procedures are inadequate in that these do not include the removal of the HEPA Filter covers and air return grates. For example, on 10/23/98, your firm was processing Carbon (#T1378) in the "Clean Room," and our investigators observed that the air supply and return covers were coated with a black powder.

2. You have no assurance that the cleaning effectiveness for the multi-use equipment in the "Clean Room," made prior to processing active pharmaceutical ingredients, nutritionals, and industrial chemicals was performed adequately. In addition, you have not validated the analytical methods for identifying product residues and could not provide scientific rationale for sampling sizes to determine the presence of residuals.

3. The manufacturing areas are not designed and/or controlled to minimize potential chemical contamination/cross contamination. For example, you manufacture PTFE [polytetrafluoroethylene (generic Teflon)], an industrial chemical, directly outside the "Clean Room." The industrial micronizing process is run continuously, and is located immediately outside the "Clean Room" and gowning room entrance. Both the "Clean Room" and the gowning room have a door that opens directly into the PTFE micronizing area. The doors are used routinely to bring in materials, equipment, and personnel. On 10/19/98 and 10/23/98, our investigators observed large amounts of thick white powder (identified as PTFE) coating the floor adjacent to the "Clean Room," the equipment, and fixtures outside the "Clean Room" bay door and the gowning room area. Your personnel were observed moving in and out of the "Clean Room," tracking this white powder (PTFE) into the area. You do not have a specific test method for the insoluble PTFE to evaluate this potential cross contaminate.

4. You failed to establish specifications for the level of cleanliness of the "Clean Room" required prior to the manufacture of an API. You have no procedure for, nor any documentation of, the evaluation performed by the Quality Unit to release the room for use in API manufacturing.

5. The Quality Unit failed to identify and document discrepancies by your production personnel. There is no assurance that adequate cleaning and release of equipment and facilities has been conducted prior to processing of APIs. For example:

a. The batch record for Sulfanilamide (T1193) revealed discrepancies between the batch cleaning sheets and the Equipment History Logbook. A review of the batch record cleaning sheet for the [redacted] indicated that the previous product manufactured was HD-RED 40 LD-FP (FD&C Red 40). The Equipment History Log identified the previous product manufactured using the [redacted] was Sulfanilamide (T0997-T0999) and T1001. Additionally, during the review of Sulfanilamide (T1193), the batch record cleaning sheet for the [redacted] noted the previous product was Fluoroethylene polymer. The Equipment History Log for the [redacted] indicated that Cobalt (T1101) was manufactured previously.

b. The batch record for Clozaphine (T1373) revealed that the operator documented two cleanings of the [redacted]. There was no documentation to support cleaning of the [redacted] (also used in the process). The incorrect documentation was confirmed by a second operator in the Equipment History Logbook and the batch record was then reviewed by the Quality Unit on 10/9/98.

c. The batch record for Bismuth Formic (T1343) revealed that the [redacted] sheet was used to document cleaning of the [redacted]. These two pieces of equipment have different cleaning procedures. The operator verified his completion of the cleaning steps for the [redacted] when he was actually cleaning the [redacted]. The batch record was reviewed by the Quality Unit on 7/18/98.

d. The Pharmaceutical Room Cleaning Sheet contained in the batch record for Bismuth Formic Iodide (BFI), T1343, indicated that the room was cleaned on 7/14/98 to remove the previous product "FLT 401" (an industrial chemical). However, the Room Cleaning and Use Log contains no entry to document the room cleaning or subsequent use of the room for processing BFI (an active pharmaceutical ingredient). The batch record was reviewed by the Quality Unit on 7/18/98.

6. You failed to perform an adequate investigation or implement any corrective action regarding deviations noted during manufacturing of active pharmaceutical ingredients. For example:

a. You rejected two lots of the API Noveon CA-1 (lot T1281 and T1282) on 6/1-2/98, due to contamination with extraneous metal pieces which was discovered when the equipment failed during processing. You have no documentation of the rejection of these two lots, other than a memo regarding their financial losses, due to the equipment damage. No investigation was conducted to identify the source of the metal contaminant, nor was any corrective action plan initiated to prevent future occurrences. The above referenced memo was not made part of the batch documentation.

b. [redacted] (an industrial Chemical) prior to processing Bismuth Formic Iodide (an API), contained a white residue for the [redacted]. A note on the Cleaning Validation Certificate of Analysis indicated that different lots of water, which were used for rinsing, was the source of the contamination. There was no documentation of the use of two different lots of water to perform the testing.

7. The process validation for the product Sulfanilamide is inadequate in that the process validation batches [T0775 (9/19/96), T0776 (9/20/96), and T0777 (9/22/96)] were manufactured without documentation of the use of the Accurate Feeder, that is identified in their current Master Batch Record.

   In addition, the batch records for FD&C Red 40 (T1188), that was manufactured just prior to the Sulfanilamide cleaning validation batches, could not be located to assure that appropriate cleaning was performed on the equipment in the "Clean Room." You also have no cleaning validation data to support the cleaning process for FD&C Red 40.

8. The active pharmaceutical ingredient Noveon (calcium polycarborphil) is processed continuously for consecutive batches, resulting in commingling of two lot numbers for one drum. The last drum of each batch and the first drum of the next consecutive batch are commingled. You do not perform a line clearance or cleaning between batches. There are no written recall procedures detailing lot traceability and timeframes for notification of customers.

9. You have failed to qualify all equipment used in the manufacture of APIs. For example, you have not qualified the photohelic gauge, which visually notifies operators of a loss of positive pressure in the "Clean Room", and the magnahelic gauge, which monitors the pressure differential between the "Clean Room" and the warehouse.

The above identification of violations is not intended to be an all-inclusive list of deficiencies observed at your facility at the time of the inspection. It is your responsibility to assure adherence with CGMP. We request that you take prompt action to correct any noted violations not already corrected and undertake, as promised, a comprehensive evaluation of your CGMP compliance. Failure to promptly correct these violations may result in a regulatory action without further notice. This includes seizure and/or injunction.

Federal agencies are advised of the issuance of all Warning Letters regarding drugs and devices so that they may take this information into account when considering the award of contracts. In addition, pending new drug applications (NDAs), abbreviated new drug applications (ANDAs) or export approval requests may not be approved until the aforementioned CGMP violations are corrected.

You should notify this office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Your reply should be sent to the Food and Drug Administration, Waterview Corporate Centre, New Jersey District Office, 10 Waterview Blvd, 3rd Floor, Parsippany, New Jersey 07054, Attention: Andrew Ciaccia, Compliance Officer.

Sincerely,

Edward H Wilkens, Jr

Douglas Ellsworth
District Director
New Jersey District Office

RELEASE

REVIEWED BY AC 6/10/99
C.O. DATE